

### **REMARKS**

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

#### ***Status of the Claims***

Upon entry of the present Amendment, claims 1-21, 23, 24, 26-28 and 30-45 are currently pending in the present application. The Office Action is final. Claims 1-20, 40 and 41 are withdrawn from further consideration as being directed to a non-elected invention.

Claims 21 and 23 have been amended without prejudice or disclaimer of the subject matter contained therein. No new matter has been added by way of the amendments. For instance, claims 21 and 23 have been amended to further define and clarify the invention. Thus, no new matter has been added. Also, no new issues have been raised by way of the present submission which presents the Examiner with the burden of additional search and/or consideration. Moreover, these amendments materially reduce issues and/or place the application into better form for appeal. Thus, entry of the present Amendment is proper and respectfully requested.

#### ***Issues Under 35 U.S.C. § 103(a), Obviousness***

Claims 21, 23, 24, 26-28, 30-39 and 42-45 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu *et al.*, U.S. Patent Application Publication No. 2002/0137211, (hereinafter, "Liu"), in view of Zhao *et al.*, *Acta Biochimica et Biophysica Sinica*, 33(1):112-116,

2001 (hereinafter, “Zhao”), Zhang *et al.*, *Acta Biochimica et Biophysica Sinica*, 31(2):119-123, 1999 (hereinafter, “Zhang”), and GenBank Acc. No. AF226688.

The Examiner reasserts that the nucleotides 1 to 5484 of SEQ ID NO: 23 were previously examined in rejected claim 26 and that Zhao discloses a transgenic silkworm with a genome comprising a “gene cassette” embraced by the instant claims.

The Examiner also asserts that since the claim language of claim 21, part (2), is open by using the transitional phrase “comprising,” it is therefore inclusive of sequences 1-5484 of SEQ ID NO: 23 and does not preclude additional sequences that are part of SEQ ID NO: 23, or GenBank Accession No. AF 226688 (both contained 6070 nucleotides). Therefore, the Examiner concludes that a skilled artisan having utilized the promoter sequences of GenBank Accession No. AF 226688 in a gene cassette, would necessarily include nucleotides 1-5484 of SEQ ID NO: 23 since the instant claims do not limit any sequences to only those of 1-5484.

Further, the Examiner suggests that Liu teaches an alternative approach method, providing a design choice to a skilled artisan for introducing a transgene into *Bombyx mori*, and therefore to express a heterologous protein. The Examiner further argues that the above design choice amounts to combining prior art elements according to known methods to yield predictable results. Applicants respectfully traverse.

Only in order to advance prosecution of this application, claims 21 and 23 have been amended, without prejudice or disclaimer of the subject matter contained therein, to limit part (2) to “an approximately 5500 base pair sequence consisting of nucleotides 1-5484 of SEQ ID NO:23. Applicants submit that the claims are focused on the specific nucleotide region of 1-5484 of SEQ ID NO: 23.

Thus, Applicants respectfully submit that the present invention is distinct from the cited references. As can be seen from paragraph (2) of amended claims 21 and 23, the gene cassette of the present invention contains a sequence enhancing an activity of a fibroin H chain promoter and a sequence enhancing an expression of an exogenous gene under the control by the fibroin H chain promoter.

The present inventors studied a gene cassette which enhances the expression of an exogenous gene when the exogenous gene is expressed under the control by a fibroin H chain promoter using a piggyBac transposon in a transgenic silkworm. As a result, the present inventors found, for the first time, that a sequence of 5'-terminal side of fibroin H chain gene, as described in paragraph [0062] of the present application, that "In the gene cassette for expressing an exogenous protein in the present invention, the 5' terminal portion of fibroin H chain gene is a DNA sequence having action that enhances expression of exogenous protein gene by a promoter."

In addition, as can be seen from the description in paragraph [0062] of the present application, which reads "In addition, as the region upstream from the 5' side of fibroin H chain gene promoter, namely a roughly 5.5 kbp upstream region, is considered to be the region that enhances promoter activity," the present inventors found that the activity of the fibroin H chain promoter can be enhanced by combining a fibroin H chain promoter and its upstream sequence (total about 5.5 kbp). In addition, the present inventors found that these elements are essential for expression of an exogenous gene using the piggyBac transposon in the silk gland of a transgenic silkworm. Hence, the present invention was completed on the basis of the above-mentioned new findings.

On the other hand, the gene cassette disclosed in the Liu reference uses fibroin L chain (not H chain as in the present invention), and does not describe or suggest the above-mentioned features of the present invention.

Next, in regards to the Liu and Zhao references, Zhao and Zhang describe a gene cassette containing a 5' terminal sequence of fibroin H chain. However, the purpose of the sequence is in the construction of a transgenic silkworm by homologous recombination of genes. Zhao and Zhang do not describe or suggest that the sequence in question has a function for enhancing expression of an exogenous gene in the silk gland. Additionally, the gene cassette of Zhao and Zhang does not contain a region enhancing the expression of promoter activity, upstream of the fibroin H chain promoter.

Also, the Examiner asserts that if genomic sequences around the fibroin H chain gene are known in GenBank Accession No. AF226688, "There is no reason for a person of ordinary skill in the art to utilize a minimal promoter region with low expression activity as part of a gene cassette to express a gene of interest in the silk gland."

Applicants respectfully disagree. In the field of the biotechnology, generally, it is well known in the art that there is a high level of unpredictability. Further, none of the disclosures of the references provide any rationale for identification of a specific region having a specific function from a genomic sequence. There would be no reasonable expectation of success due to such unpredictability. *See* M.P.E.P. § 2143.02.

For example, for the present invention, the identification of an upstream region of the fibroin H chain promoter, which enhances the expression of an exogenous gene in the silk gland on the basis of genomic sequence information, was not predictable. Finding a region of a 5'

terminal side of the fibroin chain gene that enhances the expression of an exogenous gene required a high level of the creativity due to the unpredictable nature of gene expression from a gene construct. Therefore, the Examiner's assertion is incorrect.

As can be seen from the above, if the transgenic silkworm construction system using piggyBac transposon described in the Liu reference and the gene cassette described in the Zhao and Zhang references, there is a level of unpredictability such that a skilled artisan would not be able to predict that a sequence of 5' terminal side of the fibroin H chain gene is essential for enhanced expression of an exogenous gene. Thus, the instant rejection is improper.

In addition, due to the unpredictable nature in the art, the combined teachings of the Liu reference and the genomic information around the fibroin H chain gene disclosed in Genbank Accession No. AF226688 would not render the present invention obvious since a skilled artisan would not have identified an upstream sequence of the fibroin H chain promoter that provides enhancement of the expression of an exogenous gene.

There is no disclosure within the cited references that would lead the biochemist/biologist to identify the upstream region of the fibroin H chain promoter, which enhances the expression of an exogenous gene in the silk gland on the basis of genomic sequence information, from an infinite set of sequences.

As indicated above, the present application shows that the activity of the fibroin H chain promoter can be enhanced by combining a fibroin H chain promoter and its upstream sequence (total about 5.5 kbp). In addition, the present inventors found that these elements are essential for expression of an exogenous gene using the piggyBac transposon in the silk gland of a transgenic silkworm. On the other hand, the gene cassette disclosed in the Liu reference uses

fibroin L chain (not H chain as in the present invention), and does not describe or suggest the above-mentioned features of the present invention (as admitted by the Examiner on page 7 of the previous Office Action dated April 18, 2007). Zhao and Zhang describe a gene cassette containing a 5' terminal sequence of fibroin H chain. However, the purpose of the sequence is in the construction of a transgenic silkworm by homologous recombination of genes. Zhao and Zhang do not describe or suggest that the sequence in question has a function for enhancing expression of an exogenous gene in the silk gland. Additionally, the gene cassette of Zhao and Zhang does not contain a region enhancing the expression of promoter activity, upstream of the fibroin H chain promoter.

In light of the above presently amended claims and remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 U.S.C. § 103(a). Based upon the above, it is respectfully submitted that a *prima facie* case of obviousness has not been established. Applicants respectfully request reconsideration and subsequent withdrawal of the above rejections.

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

### **CONCLUSION**

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present

application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

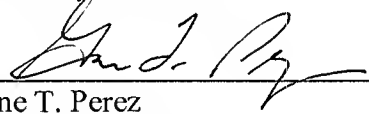
In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Eugene T. Perez, Reg. No. 48,501, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: April 3, 2009

Respectfully submitted,

By  \_\_\_\_\_  
Eugene T. Perez

Registration No.: 48,501  
BIRCH, STEWART, KOLASCH & BIRCH, LLP  
8110 Gatehouse Road  
Suite 100 East  
P.O. Box 747  
Falls Church, Virginia 22040-0747  
(703) 205-8000  
Attorney for Applicants